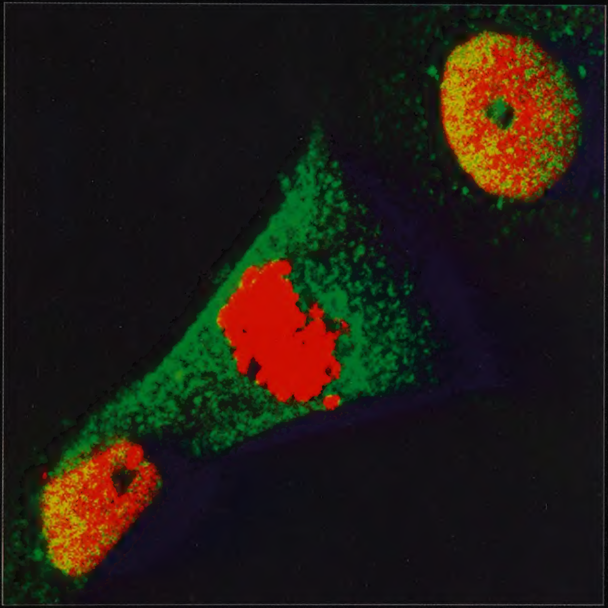

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Institute of Cancer and Developmental Biology

UNIVERSITY OF CAMBRIDGE

1997

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University of Cambridge

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Front Cover Photograph

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Redistribution of *Xenopus laevis* XOrc1 protein in mitotic cells. XOrc1 (green) overlaps with DNA staining (red) in two interphase cells. In the mitotic cell a proportion of XOrc1 is present in the cytoplasm.

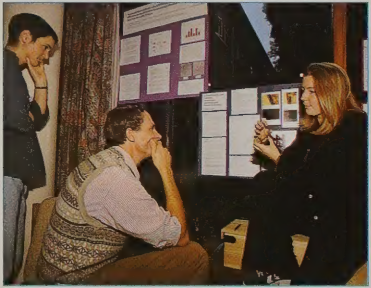
FOREWORD BY THE CHAIRMAN

HISTORICAL BACKGROUND The Institute is situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance of the centre of the historic city. It was founded in 1989 to promote research in the areas of Developmental Biology and Cancer Biology and is an assemblage of independent research groups located in one building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned with how cells come to acquire and maintain their ***normal*** function; cancer is a result of a cell breaking loose from its correct controls and becoming ***abnormal***. Both areas require a detailed knowledge of intracellular processes, which need to be analyzed at the cellular and molecular levels.

These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires a knowledge of the processes which ensure correct cell function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques which no one person can master, such as gene cloning, antibody preparation, cell culture, and embryological manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.

WITHIN THE INSTITUTE Now in its fully operational sixth year, our Institute consists of sixteen independent research groups containing postdoctoral scientists, visitors, research assistants and a total of more than 40 graduate students. Together with support staff, the Institute comprises almost 200 personnel, all of whom are affiliated through their group leaders to one of the University science departments. The teaching we do and our lists of publications are credited to our parent departments, and we have access to their workshops and equipment.

We receive funding in a 2:1 ratio from our major sponsors, the Wellcome Trust and the Cancer Research Campaign. In September 1995, a site visiting committee spent two days in the Institute listening to presentations and talking to group leaders. As a result of this visit, and of our scientific publications over the previous five years, we are very pleased indeed to say that our quinquennial core funding was fully renewed by our sponsors from January 1996.



During the course of 1996, Michael Akam, one of our senior group leaders, was promoted to professorial status by the General Board of the University, while three of our younger group leaders have moved up to senior group leader status: Steve Jackson, who accepted the University's Quick Professorship of Biology, Tony Kouzarides who was appointed University Cancer Research Campaign Reader in Molecular Cancer Biology during 1996, and Daniel St. Johnston.

In June 1996, the Institute celebrated the award of two prestigious medals of the Biochemical Society to members of this Institute. Professor Ron Laskey received the Society's CIBA Medal and Professor Steve Jackson was awarded the Biochemical Society's Colworth Medal 1997.

Sponsored by the Wellcome Trust and Cancer Research Campaign, new extensions to the south side of our building are nearing completion and are expected to be ready for occupation before the end of 1996. As a result of these extensions, we propose to recruit one or more new group leaders during the next two years. In addition, we greatly look forward to an enlarged seminar/tea room, a facility which plays a major role in promoting the scientific interactions that are so vital to any research institute.

John Gurdon.

JOHN GURDON
CHAIRMAN

INTEGRIN EXPRESSION BY NEUROEPITHELIAL PRECURSOR CELLS
Thomas S. Jacques
1 Summary
2 Characterisation of Neurospheres
4 Integrin Expression

INSTITUTE FACILITIES

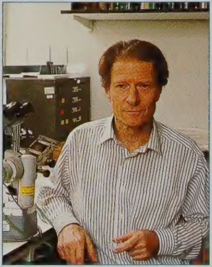
The extension to our building will provide space for an additional twenty to twenty-five research staff by creating three new laboratory areas and allowing reorganisation of administrative areas and subsequent extension of an existing laboratory. Two temperature controlled rooms will be installed in addition to improvements in seminar and meeting room space.

Our graphics facility has grown considerably over the past year, the new equipment including a second confocal microscope, video imaging equipment and silicon graphics workstation. This allows analysis and presentation of time lapse and 3 dimensional data. We are grateful to our sponsors for their generous support.

In addition to a successful football season for the Wellcome Wanderers, leisure and social events have included participation in a rounders league, basketball matches, paragliding trips and popular wine-tasting evenings. We hope that the new catering arrangements will allow gastronomic events to feature significantly in the coming year.

The evenings entertainment at the Institute's annual scientific retreat featured Philippe Gautier and his jazz/rock band seen here playing to an enthusiastic audience.

John Gurdon



ERIC BELLEFROID

DEVANAND CREASE

STEVEN DYSON

NIGEL GARRETT

NATASHA McDOWELL

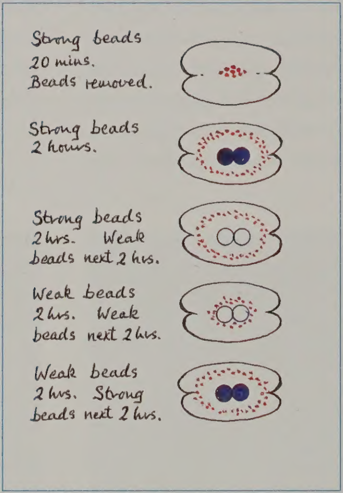
ANDREW MITCHELL

KEN RYAN

FIONA STENNARD

ELIZABETH TWEED

AARON ZORN


Strong beads 20 mins. Beads removed.
Strong beads 2 hours.
Strong beads 2hrs. Weak beads next 2 hrs.
Weak beads 2hrs. Weak beads next 2hrs.
Weak beads 2hrs. Strong beads next 2 hrs.

Activin loaded beads (blue) in animal cap sandwiches. Cells express Xbrachyury (red) by a ratchet-like mechanism.

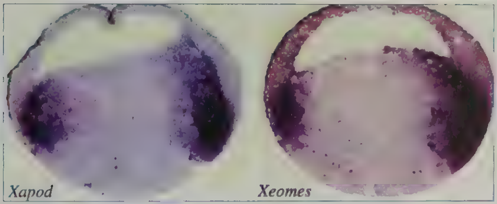
GURDON, J.B., HARGER, P., MITCHELL, A., and LEMAIRE, P. (1994). Activin signalling and the spatial control of response to embryonic induction. **Nature 371,** 487-492.

STENNARD, F., CARNAC, G. and GURDON, J.B. (1996). The *Xenopus* T-box gene, *Antipodean*, encodes a vegetally localised maternal mRNA that can trigger mesoderm formation. **Development, 122,** 4179-4188.

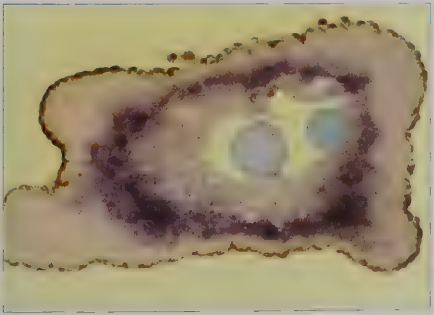
RYAN, K., GARRETT, N., MITCHELL, A., and GURDON, J.B. (1996). Eomesodermin, a key early gene in *Xenopus* mesoderm differentiation. **Cell, 87,** 989-1000.

For further publications see no. 10, 11, 15, 28, 29, 30, 31, 80.

MECHANISMS OF CELL DIFFERENTIATION IN EARLY AMPHIBIAN DEVELOPMENT



Two new T-domain genes are transcribed as very early responses to activin signalling.



Cells expressing Xbrachyury (purple) are located several cell diameters away from the activin-containing bead.

The early development of Vertebrates depends to a very large extent on cell interactions. Typically these involve the synthesis and secretion of protein signalling molecules from cells in one position in an embryo and their receipt by other cells elsewhere. The receiving cells activate genes and undergo differentiation as a result of the signalling process.

We have devised experimental combinations of signalling and responding cells to analyse how a concentration gradient of activin (a TGFβ class of signalling molecule) induces different kinds of gene activity. We see the transcription of early response genes as little as two hours after supplying the activin signal. We are able to control the concentration and time of action of the inducing signal using activin beads, and to influence cell responsiveness by over- or under-expressing activin receptors or dominant negative forms of them. We have recently identified two new early response genes both belonging to the T-domain class of transcription factors. Activin signalling is likely to be part of the natural mesoderm inducing signal in vertebrate development.

The mesoderm-forming induction is immediately followed in Xenopus by community effects in the notochord and muscle and by an inhibitory influence of ventral ectoderm - these processes are believed to refine early responses to a morphogen gradient by increasing uniformity within, and demarcation between, mesodermal cell-types. We are actively engaged in trying to identify new genes responsible for these various mesodermal activities, using a functional screen of subtracted cDNA libraries.

MICHAEL AKAM

GUILLAUME BALAVOINE

SUSAN BEGG

CHARLES COOK

CHUN-CHE CHANG

OLENKA DUNIN-BORKOWSKI

FRANCESCO FALCIANI

PHILIPPE GAUTIER

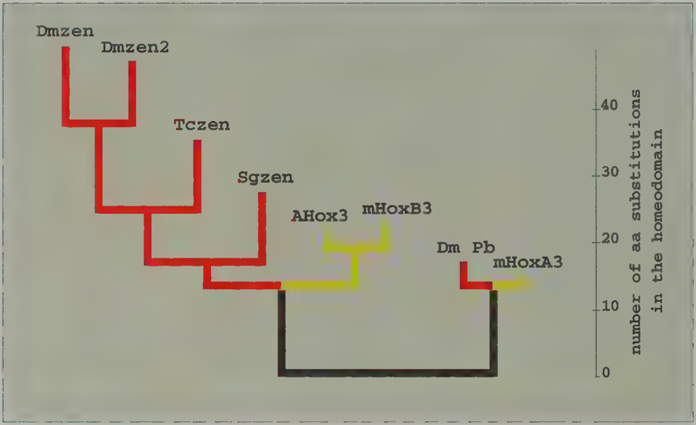
MIODRAG GRBIC

MARION ROZOWSKI

LOUISE SMITH

DAVID STERN

BEVERLEY YEN



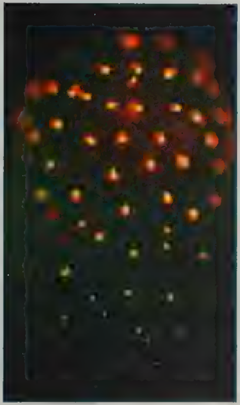
Hox genes that got away.
We infer that rapid divergence of an ancestral class 3 homeobox gene gave rise to the Drosophila zen genes, which mediate D/V patterning. Ancestral sequences and sequence divergence are inferred by comparing grasshopper (Sg) beetle (Tc) and fly (Dm) zen genes with their closest chordate homologues (yellow, mouse and amphioxus).

AVEROF, M. and AKAM, M. (1995). Hox genes and the diversification of insect and crustacean body plans. **Nature 376**, 420-423.

FALCIANI, F., HAUSDORF, B., SCHRÖDER, R., AKAM, M., TAUTZ, D., DENELL, R. AND BROWN, S. (1996). Class 3 Hox genes in insects and the origin of *zen*. **Proc. Nat. Acad. Sci. USA 93**, 8479-8484.

For further publications see no. 2, 19.

HOX GENES AND SEGMENT PATTERNING IN ARTHROPODS

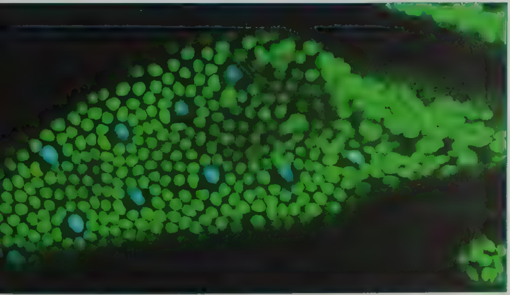


Locust egg at early cleavage stages after injecting fluorescent dye into the yolk. Each cleavage nucleus (yellow/green) is surrounded by an island of cytoplasm, which has accumulated the injected dye (red), showing that the egg is still syncytial.

Hox genes encode transcription factors that specify the position of cells along the antero-posterior axis of the embryo. In arthropods, they control the diversification and specialisation of segments.

It is still a mystery how the Hox genes control the final morphology of each segment. To address this question, we are studying what cellular processes result in the different shapes and sizes of the three legs of Drosophila, and how these processes are modulated by the differential expression of the Hox genes.

In Drosophila, the Hox genes are activated in the correct segments by the products of segmentation genes. These form intracellular gradients in the earliest stages of development, while the embryo remains syncytial. Many other insects, and most other organisms, do not have a persistent syncytial stage of development. In locusts, for example, we have recently shown that the cells of the embryo become isolated from one another at very early stages of cleavage. To investigate how patterning occurs in this cellular environment, we are analysing the expression of other patterning genes, and attempting to manipulate their expression in the early embryo.



Nuclei in the developing leg of a fly, visualised within the live pupa using green fluorescent protein. Each large bristle cell (blue) is surrounded by a rosette of epidermal cells.

Although Hox gene clusters are conserved in many animal phyla, some of the genes within the insect Hox clusters appear to have escaped from stringent selection, evolving rapidly to acquire new functions, particularly in early development. We have shown that the zen class of dorsal/ventral patterning genes are highly divergent Hox class 3 genes. We are studying these and other divergent Hox genes to establish where in the phylogenetic tree their new functions arose, and how their regulation has changed.

ANDREA BRAND

ROBERT BARBOSA

TORSTEN BOSSING

CATHERINE DAVIDSON

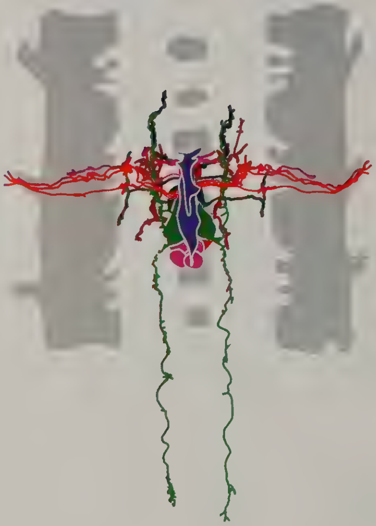
EMMA-LOUISE DORMAND

NEIL HAYWARD

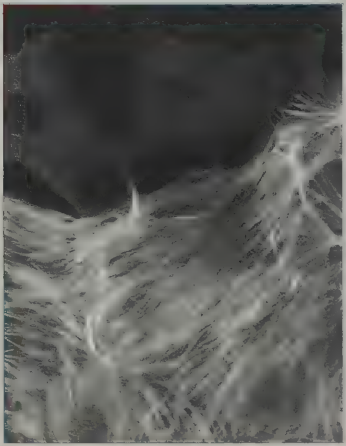
ALICIA HIDALGO

ULRIK JOHN

ALISON SCHULDT



The midline progenitors give rise to all three neural cell types: interneurons, motor neurons and glia. These cells arise from five distinct classes of cell lineage, each depicted in a different colour.

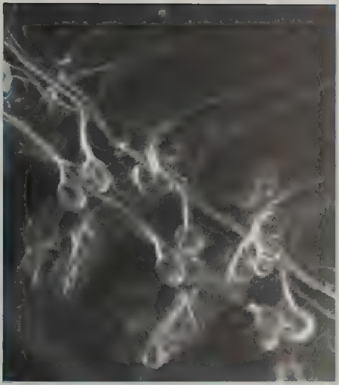


Tau-GFP binds to microtubules, highlighting the cytoskeleton within each epidermal cell of a living larva.

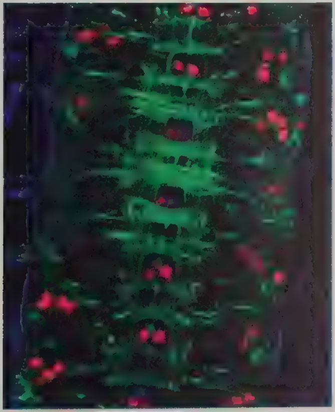
BRAND, A.H. (1995) GFP in *Drosophila*. **Trends in Genetics 11,** 324-325.

HIDALGO, A., URBAN, J. and BRAND, A.H. (1995) Targeted Ablation of the Longitudinal Glia Disrupts Axon Tract Formation in the *Drosophila* Embryonic CNS. **Development 121,** 3703-3712.

EMBRYONIC NERVOUS SYSTEM DEVELOPMENT IN *DROSOPHILA*



rgeted expression of Tau-GFP in motor neurons and nterneurons enables idual neurons to be raced as they extend axons in the central ous system of living embryos.



GFP continues to fluoresce after fixation (green), which allows counterstaining with antibodies that recognise other markers (in red and blue).

During nervous system development each neuron acquires a specific identity, directing it to extend an axon towards and synapse with an appropriate target cell. Cell identity is acquired in response to a specific pattern of gene expression and to cell-cell interactions. We have developed a general method for directed gene expression in *Drosophila*, the GAL4 system, that allows transcription to be manipulated both spatially and temporally. Using targeted gene expression, transcription patterns in neuronal precursor cells and in their progeny can be altered with the aim of eliciting specific cell fate changes. Directed expression of diphtheria toxin or ricin can be used to ablate cells and to eliminate the cell-cell interactions that may influence cell identity and axon outgrowth.

We are using targeted cell ablation to study the role of glial cells and pioneer neurons in establishing the axon scaffold. We are also killing specific subsets of the ventral midline cells, which may send out attractive or repulsive signals to migrating axons. For this reason the midline cells are thought to be analogous to the vertebrate floorplate.

To monitor the effect of cell ablation and cell fate changes *in vivo*, we are labelling neurons and glia in living embryos by expression of green fluorescent protein (GFP) from the jelly fish, *Aequoria victoria*. We can now assay cell-cell interactions *in vivo*, tracing individual cells through embryonic development.

NICK BROWN

INÉS ALVAREZ-GARCÍA

JAMES BLOOR

STEPHEN GREGORY

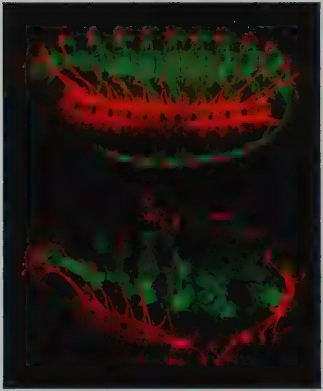
ANDREA KNOX

ANNE MAELAND

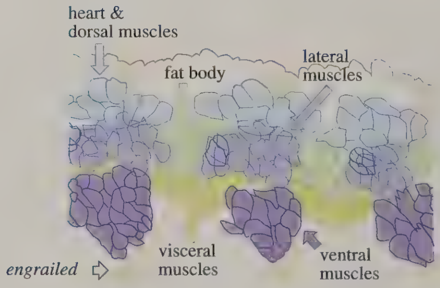
LOLA MARTIN-BERMUDO

JOHN OVERTON

PHIL WALSH



Defects in morphogenesis are found in embryos mutant for the gene encoding the β_{ps} *intergrin subunit. A normal embryo (top) and a mutant embryo (bottom) are stained to show the muscles (green) and the nervous system (red)*

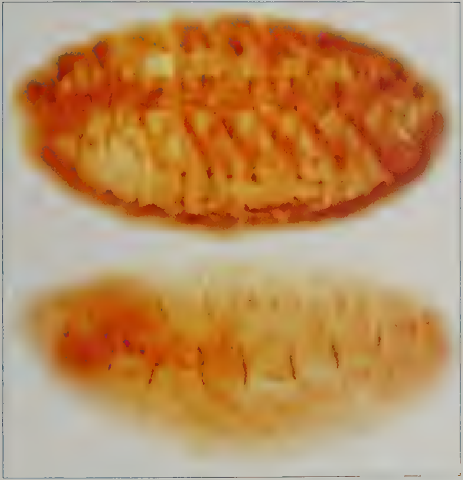


Identification of the progenitors of the different muscle derivatives by visualising cell shape with the marker CD2.

DUNIN-BORKOWSKI, O.M., BROWN, N.H. and BATE, M. (1995). Anterior-posterior subdivision and the diversification of the mesoderm in *Drosophila*. **Development 121**, 4183-4193

MARTIN-BERMUDO, M.D. and BROWN, N.H. (1996). Intracellular signals direct integrin localization to sites of function in embryonic muscles. **J. Cell Biol. 134**, 217-226

MOLECULAR ANALYSIS OF CELL ADHESION



Mapping a domain of the β_{PS} *protein that can shift the localisation of the CD2 protein from uniform expression of the muscle cell surface (top) to the ends of the muscles (bottom) where the* β_{PS} *intergrin is normally found.*

The development of a multicellular organism requires numerous molecular interactions between proteins on the cell surface. These proteins mediate both adhesion and signalling between cells. Our aims are to characterise the cellular interactions and shape changes that occur during the development of the fruit fly *Drosophila*, identify the proteins that mediate these events and understand how they function.

We have developed a new marker that allows us to see the shapes of cells within the developing embryo. By generating embryos that express this marker in the developing mesoderm we have been able to see how cell shape changes accompany the early segregation of the populations of cells that give rise to the different mesodermal derivatives. We now wish to identify the proteins that specify the changes in shape and adhesiveness that accompany this segregation.

Members of the integrin family of adhesion receptors are required for the adhesion of different cell layers to each other in the developing embryo. By manipulating the genes encoding these integrins we are examining how these proteins function to achieve this. We have found to our suprise that in the embryo the localisation of integrins to their sites of function can be directed from inside the cell, rather than simply directed by binding to a localised extracellular ligand. We have recently completed a screen for mutations in genes which are required for integrin mediated adhesion, and have identified 10 new genes. The cloning and characterisation of these genes will illuminate the links between the inside and outside of the cell.

MARTIN EVANS

STELLA BROWN*

MARK CARLTON

HELEN CHILVERS

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CATHERINE GODDARD*

SUSAN HUNTER

GHOLSON LYON

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ANDREAS RUSS

EMILY SCOTT

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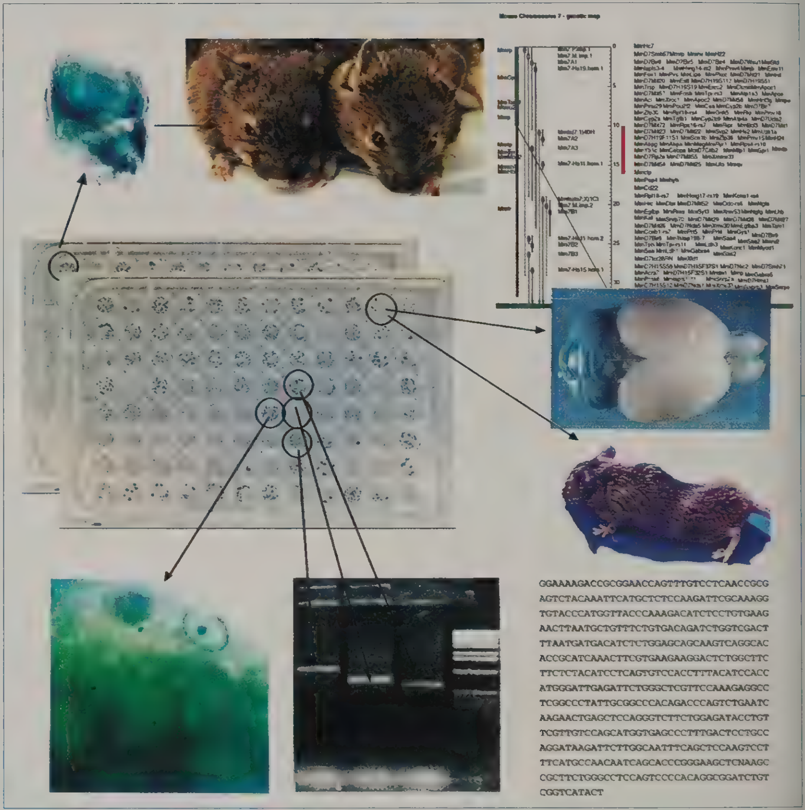
FIONA THISTLETHWAITE

ROSEMARY THRESHER*

JOANNE WILSON

MAGDALENA ZERNICKA-GOETZ

We continue to work in collaboration with BILL COLLEDGE'S group* in the Department of Physiology


Mouse Chromosome 7 - genetic map
GGAAAAGACCGCGGAACCAGTTTGTCCTCAACCGCG
AGTCTACAAATTCATGCTCTCCAAGATTCGCAAAGG
TGTACCCATGGTTACCCAAAGACATCTCCTGTGAAG
AACTTAATGCTGTTTCTGTGACAGATCTGGTCGACT
TTAATGATGACATCTCTGGAGCAGCAAGTCAGGCAC
ACCGCATCAAACTTCGTGAAGAAGGACTCTGGCTTC
TTCTCTACATCCTCAGTGTCCACCTTTACATCCACC
ATGGGATTGAGATTCTGGGCTCGTTCCAAAGAGGCC
TCGGCCCTATTGCGGCCCACAGACCCAGTCTGAATC
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TCGTTGTCCAGCATGGTGAGCCCTTTGACTCCTGCC
AGGATAAGATTCTTGGCAATTTCAGCTCCAAGTCCT
TTCATGCCAACAATCAGCACCCGGGAAGCTCNAAGC
CGCTTCTGGGCCTCCAGTCCCCACAGGCGGATCTGT
CGGTCATACT

VERLHAC, M.H., KUBIAK, J.Z., WEBER, M., GERAUD, G., COLLEDGE, W.H., EVANS, M.J. and MARO, B.1996. MOS is required for MAP kinase activation and is involved in microtubule organization during meiotic maturation in the mouse. **Development 122**, 815-822.

HAYMAN, A.R., JONES, S.J. BOYDE, A., FOSTER, D. COLLEDGE, W.H., CARLTON, M.B.L., EVANS, M.J. and COX, T.M. 1996. Mice lacking tartrate-resistant acid phosphatase (Acp5) have disrupted endochondral ossification and mild osteopetrosis. **Development 122**, 3151-3162

For further publications see no. 16, 22, 38, 80.

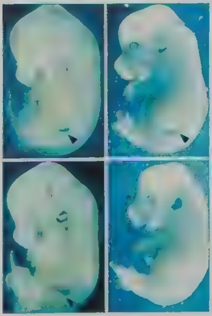
Mammalian Developmental Biology and Genetics through the Culture of Embryonic Stem Cells

Diagram illustrating one of our gene-trap experiments. The original multiwell plate no.14 shows ES cell colonies stained for lac-z expression. (note well 14E8 is empty - the cells were trypsinised and passaged from this particular dish before staining) Clone 1A1 shows extensive expression in the 7.5 day egg cylinder and the resulting mice show a phenotype of a foreshortened face. The map position of this locus is shown. 14E7 shows a specific pattern of expression including maturing oocytes. 5'cDNA race products are shown for ES cell clones 14D8, 14E8 and 14F8 with one of the sequences. An ataxia is associated with mice derived from 14A11 and the locus is expressed in the cerebellum.

We have been exploring the use of Green Fluorescent Protein for expression in mice. A modified form of GFP under the cdc2 promoter was introduced into ES cells and clones isolated which show expression. This figure shows a six day old chimaeric embryo made with GFP expressing ES cells and developed in utero. Two superimposed confocal images showing green fluorescence in the green channel and overlaid non specific fluorescence in the red channel.

Our overall strategy and interest is in an Experimental Mammalian Genetics which is made possible through manipulation of the mouse embryo in particular by the availability and use of embryonic stem (ES) cells. As these cells provide a bridge between the whole animal and tissue culture, specific genetic modification which may be induced, screened or selected in culture can be tested and recombined within the context of the physiology and genetics of the whole animal.

We are creating mouse mutants resulting from random integration of viral DNA into the genome and are using homologous recombination to introduce specific mutations into ES cells. We have a broad range of projects from those where we are still aiming to improve the embryo and genetic manipulation technology to the very applied use of animal models of human disease and in particular of cystic fibrosis which has led us on into attempting to apply genetic manipulation in the inverse direction – i.e. gene therapy.



Hox 11 in spleen development: Lac-Z staining (under the control of Hox 11) shows onset of spleen development.

CHARLES FFRENCH-CONSTANT

KATHARINE BLASCHUK

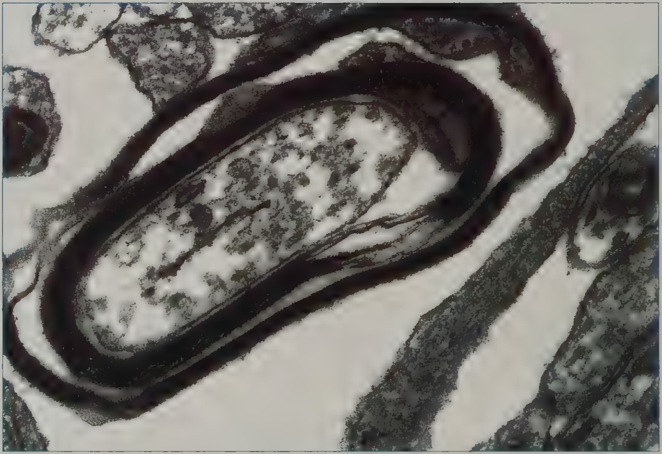
PHIL BUTTERY

EMMA FROST

THOMAS JACQUES

MONIQUE JOUET

MARCO PONASSI



Myelin sheath formation in xenocultures of mouse oligodendrocytes and rat neurons

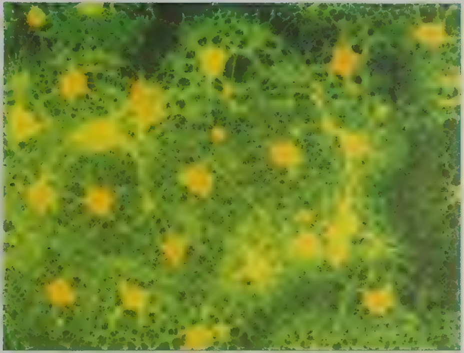
KIERNAN, B.W., GOTZ, FAISSNER, A. and FFRENCH-CONSTANT C. 1996. Tenascin-C inhibits oligodendrocyte precursor migration by both adhesion-dependent and adhesion-independent mechanisms. **Mol. Cell. Neurosci. 7**, 322-335.

MILNER, R., EDWARDS, G., STREULI, C., and FFRENCH-CONSTANT, C. 1996 A role in migration for the $\alpha\nu\beta_1$ integrin expressed on oligodendrocyte precursors. **J. Neurosci. 16**, 7240-7252.

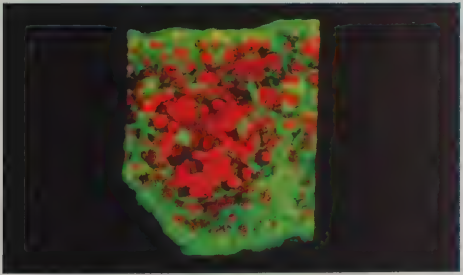
SHAW, C.E., MILNER, R., COMPSTON, A.S., FFRENCH-CONSTANT, C. 1996 Analysis of Integrin Expression on oligodendrocytes during Axo-Glial interaction by using Rat-Mouse Xenocultures. **J. Neurosci. 16** (3), 1163-1172.

For further publications see no. 20, 21, 58.

CELL EXTRACELLULAR MATRIX INTERACTIONS DURING NEURAL DEVELOPMENT



Oligodendrocytes in cell culture



A confocal slice through a ball of neuroepithelial cells (a neurosphere)

The central nervous system (CNS) develops from a simple two-dimensional sheet of cells into a complicated three-dimensional structure. The early part of this development can be sub-divided into three basic stages; proliferation of uncommitted neural precursors, migration of differentiated progenitors and differentiation. A better understanding of these stages is important both for the study of developmental defects and also to enhance repair in the damaged CNS.

Our lab examines the role of extracellular matrix molecules and their integrin receptors in these stages. We use two model systems; neurospheres (see figure) to examine the behaviour of neural precursor cells and oligodendroglial cells to examine the later stages of migration and differentiation. Both cell types can be grown in culture facilitating cell and molecular biological analyses of integrin-ECM interactions.

We have shown that integrins and ECM molecules contribute to the regulation of cell migration in the developing CNS. One of these integrins, $\alpha\nu\beta_1$, is lost during oligodendrocyte precursor differentiation, suggesting a role in the timing of migration. Current experiments to determine the role of this and other integrins using a combination of antibody blocking, peptides, transfection of chimaeric integrins and transplantation are in progress.

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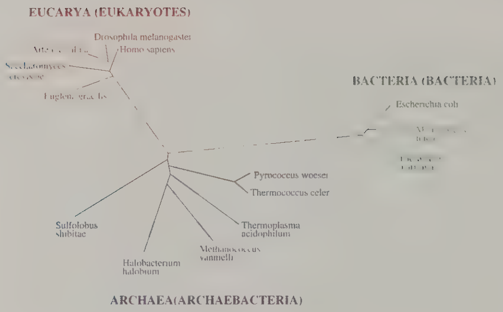
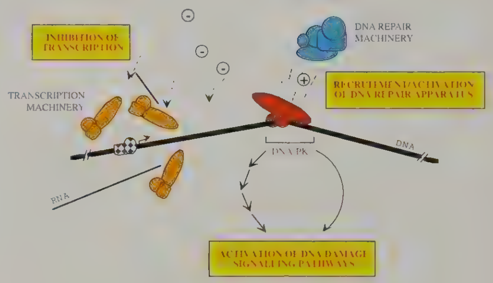
HELEN REED
SCOTT ROTTINGHAUS
JOHN ROUSE
GRAEME SMITH
SOO-HWANG TEO
UGUR YAVUZER



Archaea (archaebacteria): the third primary domain of life. Despite lacking nuclei and being similar to eubacteria in morphology, Archaea ar at least as as distant evolutionarily from Bacteria as they are from eukaryotes. Nevertheless, through cloning archaeal transcription factors and establishing a defined in vitro transcription system, we have discovered striking similarities betwee transcription in Archaea and in eukaryotic cell nuclei.

DNA-PK: A paradigm for DNA damage sensing systems. DNA-PK binds to a DNA double-strand break (DSB) and is viewed as potentiating DNA repair through recruiting and activating the DNA repair apparatus, by interfering with transcription, and/or by triggering DNA damage signalling pathways.

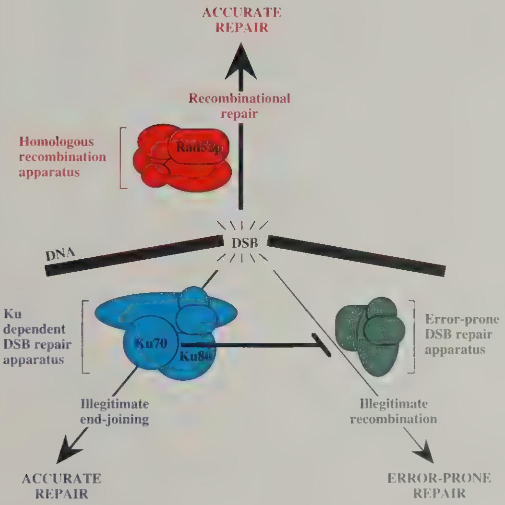

INHIBITION OF TRANSCRIPTION
DNA REPAIR MACHINERY
RECRUITMENT/ACTIVATION OF DNA REPAIR APPARATUS
TRANSCRIPTION MACHINERY
DNA
DNA-PK
RNA
ACTIVATION OF DNA DAMAGE SIGNALLING PATHWAYS

HARTLEY, K., GELL, D., ZHANG, H., SMITH, G. C. M., DIVECHA, N., CONNELLY, M. A., ADMON, A., LEES-MILLER, S. P., ANDERSON, C.W. , and JACKSON, S. P. (1995). DNA-dependent protein kinase catalytic subunit: a relative of phosphatidylinositol 3-kinase and the ataxia telangiectasia gene product. **Cell, 82**, 849-856.

BOULTON, S. J., and JACKSON, S. P. (1996). *Saccharomyces cerevisiae* Ku70 potentiates illegitimate DNA double-strand break repair and serves as a barrier to error-prone DNA repair pathways. **EMBO J. 15**, 5093-5103.

For further publications see no. 5, 7, 8, 12, 14, 27, 33, 34, 35, 37, 49, 50, 51, 61, 72, 73, 78, 79.

DNA repair, Genetic Recombination and Transcription


ACCURATE REPAIR
Recombinational repair
Homologous recombination apparatus
Rad52p
DSB
DNA
Ku dependent DSB repair apparatus
Ku70
Ku80
Error-prone DSB repair apparatus
Illegitimate end-joining
Illegitimate recombination
ACCURATE REPAIR
ERROR-PRONE REPAIR

Ku potentiates accurate DNA double-strand break (DSB) repair. Our data suggest that there are three mechanisms for repairing DSBs. The first is homologous recombinational repair and is Ku-independent. The second, illegitimate end-joining, is Ku-dependent, and results in the ligation of DNA ends without the loss or addition of DNA sequences. The third, illegitimate recombination, is relatively ineffective and results in deletion of DNA sequences and joining via short direct repeat elements. This latter pathway does not require Ku and actually appears to be suppressed by Ku.

Our aim is to gain insights into important biological phenomena by studying the mechanisms and control of transcription and DNA repair. To this end, we are employing a combination of molecular cloning, genetics, and biochemistry in bacterial, yeast, and mammalian systems.

For example, our work has indicated how transcription by eukaryotic RNA polymerase III is regulated during the cell cycle. Furthermore, we have discovered recently that the retinoblastoma (RB) tumour suppressor protein is a potent inhibitor of transcription by RNA polymerase III. In addition, we study transcription in prokaryotes termed Archaea. Strikingly, the transcriptional machineries of Archaea and eukaryotic nuclei are fundamentally homologous, and we are using the unique biochemical advantages of Archaea to define the mechanisms and evolution of transcriptional control.

We also study how cells detect, respond, and repair damaged DNA. One major focus in this area is the the enzyme DNA-dependent protein kinase (DNA-PK), which binds to damaged DNA through a protein termed Ku. By studying Ku and DNA-PK function in yeast and mammalian systems, we have discovered that this enzyme is involved in DNA repair, genetic recombination, and telomeric length maintainence. Finally, we also work on a series of proteins that are related to DNA-PK and which also function in DNA damage detection. One of these is ATM, the protein deficient in the human cancer predisposition and neurodegenerative disease ataxia-telangiectasia. Through studying DNA-PK and its relatives, we hope to gain a better understanding of how eukaryotic cells maintain genomic stability, and determine how defects in DNA repair and DNA damage detection can lead to cancer.

TONY KOUZARIDES

ANDREW BANNISTER

ALEXANDER BREHM

CATHERINE LE CHALONY

ALISTAIR COOK

FRANCOIS FUKS

LUKE HUGHES-DAVIES

PAUL LAVENDER

KLAUS MARTIN

MARIAN MARTINEZ

DENNIS McCANCE

JONATHAN MILNER

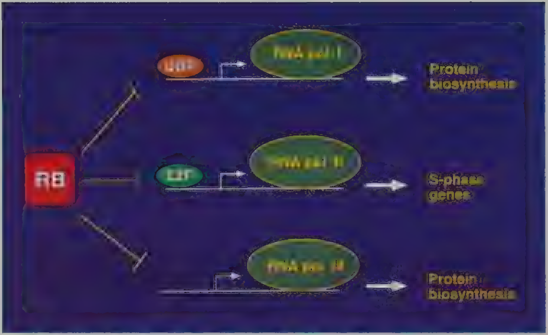
ERIC MISKA

JULIET REID

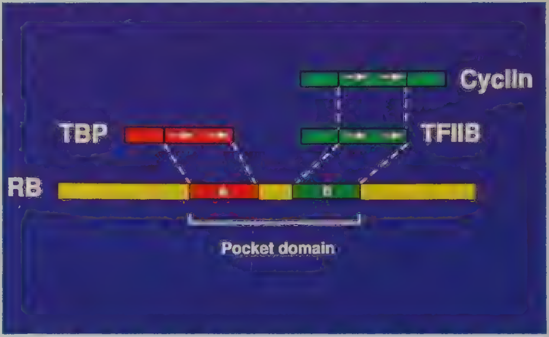
MATTHIAS SELTMANN

LAURENCE VANDEL

RB can suppress pol II genes required for S-phase as well as pol I and pol III genes required for protein biosynthesis.



The pocket domain of RB shows sequence similarity to two general transcription factors, TBP and TFIIB and to the Cyclin family of proteins

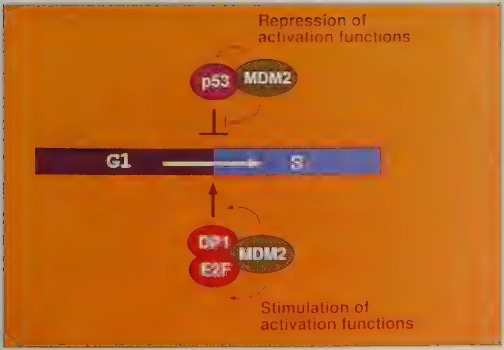


BANNISTER A.J. and KOUZARARIDES T. 1996. The CBP co-activator is a histone acetyltransferase. **Nature 384**, 641-643.

WHITE, R.J., TROUCHE, D., MARTIN, K., JACKSON, S.P. and KOUZARIDES, T. 1996. Repression of RNA polymerase III transcription by the retinoblastoma protein. **Nature 382**, 88-90.

For further publications see no. 3, 50, 54, 60, 75, 76.

Transcriptional Regulation by Oncogene products and Tumour Suppressor Proteins


Repression of activation functions
p53
MDM2
G1
S
DP1
E2F
MDM2
Stimulation of activation functions

MDM2 represses p53 and stimulates E2F1/DP1, resulting in S phase progression

Our group is interested in defining the mechanisms by which transcription factors modulate gene expression and how these functions bring about the control of cell proliferation. We are currently trying to understand how the Retinoblastoma tumour suppressor protein (RB) mediates growth arrest.

One of the well characterised functions of RB is its ability to silence the activation capacity of E2F, a transcription factor responsible for turning on S-phase specific genes. We have recently discovered that RB can also repress transcription of most genes transcribed by RNA polymerase III. This raises the interesting possibility that RB induces growth arrest not only by turning off S-phase genes but also by suppressing the protein biosynthetic pathway. We suspect that RB can repress transcription by virtue of its similarity to two general transcription factors, TBP and TFIIB.

We are now using the two hybrid assay in yeast to identify new RB targets. So far this screen has uncovered two new RB-binding transcription factors whose activity is negatively regulated by RB.

We are also trying to understand how the oncogenic E2F transcription factor mediates its functions. We have found that the transcriptional activation capacity of E2F is potentiated by the direct binding of two co-activator proteins, MDM2 and CBP, each of which have been independently implicated in the regulation of cell proliferation. CBP may mediate these functions by acting as a histone acetyltransferase.

RON LASKEY

DAWN COVERLEY

TORSTEN KRUDE

YUMIKO KUBOTA

KATHERINE MARHEINEKE

JACKIE MARR

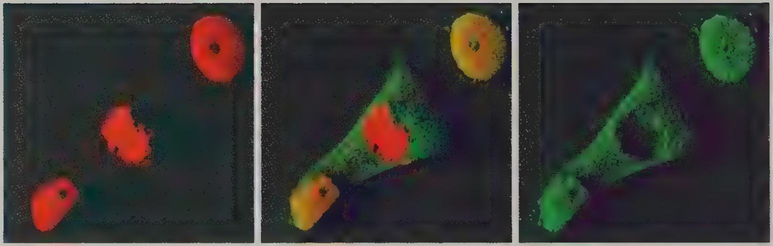
TONY MILLS

KEITA OHSUMI

PIOTR ROMANOWSKI

HANNAH WILKINSON

GARETH WILLIAMS



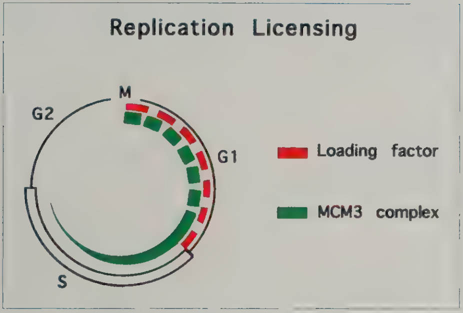
Redistribution of ORC (green) relative to DNA (red) during division of Xenopus cells (Romanowski et al., Ref. below)

GÖRLICH, D., KRAFT, R., KOSTKA, S., VOGEL, F., HARTMANN, E., LASKEY, R.A., MATTAJ, I.W. and IZAURRALDE, E. 1996. Importin provides a link between Nuclear Protein Import and U snRNA Export. **Cell 87**, 21-32.

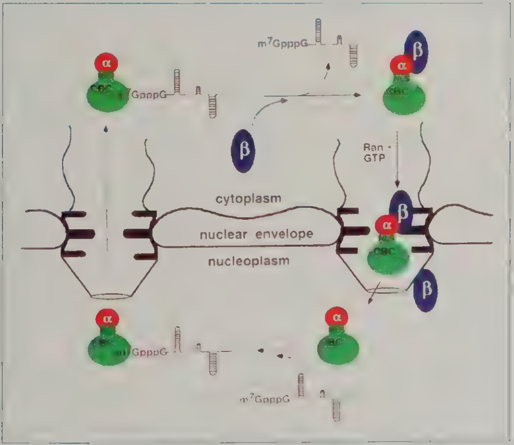
ROMANOWSKI, P., MADINE, M.A., ROWLES, A., BLOW, J.J. and LASKEY, R.A. 1996. The *Xenopus* origin recognition complex is essential for DNA replication and MCM binding to chromatin. **Current Biology 6**, 1416-1425.

For further publications see no. 13, 23, 25, 26, 45, 46, 47, 52, 53, 62, 67, 68.

CONTROL OF EUKARYOTIC CHROMOSOME REPLICATION AND NUCLEAR PROTEIN IMPORT



Two step model for replication licensing



Model for the role of importin in nuclear protein import and RNA export (Gorlich et al., Ref. below)

We are analysing the control of eukaryotic chromosome replication and the control of nuclear protein import using cell-free systems derived from eggs of *Xenopus laevis* and, more recently, human cells.

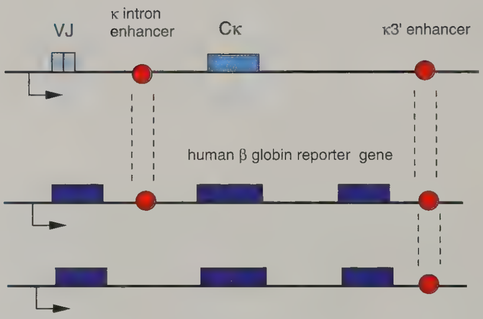
Replication is coupled to the cell cycle so that DNA replicates only once between consecutive divisions. This can be explained by a licensing factor model. We have shown that a family of known proteins, the MCM3 family, are components of the licensing system, and that another "loading" factor regulates their binding to chromatin. In collaboration with A. Rowles and J. Blow we have characterised a *Xenopus* homologue of the origin recognition complex 'ORC' and shown that it has some of the properties predicted for an MCM loading factor.

Recently, we have developed a novel cell-free system that initiates DNA replication in human cell extracts in vitro. This should allow similar levels of analysis in human cells to those achieved previously in *Xenopus*.

We have also investigated how nuclear proteins are targeted to the cell nucleus and how ribonucleoproteins (RNPs) are exported from the nucleus. We have identified a protein, importin, which acts as a receptor for nuclear localisation signals. One subunit of importin enters the nucleus with its passenger nuclear protein. The same subunit of importin (α) is implicated in RNP export. It binds the cap binding complex (CBC) on the 5' end of pol II transcripts and escorts it to the cytoplasm. Importin β then releases RNA into the cytoplasm and returns CBC to the nucleus.

Kerstin Meyer

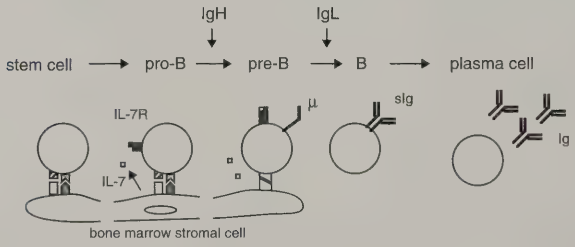
JOHN IRELAND



Structure of contructs introduced into transgenic mice

Structure of constructs introduced into transgenic mice.

Schematic representation of B cell development.

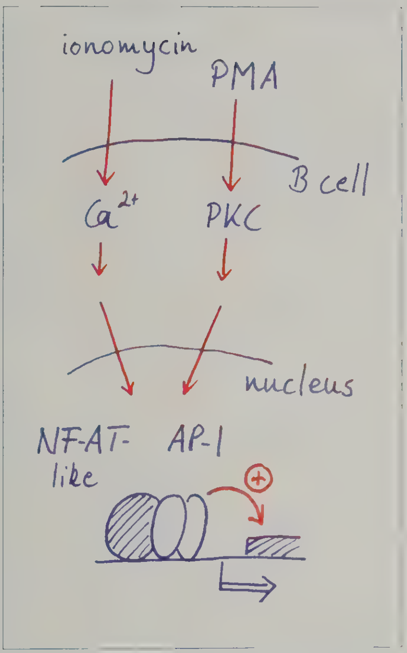


MEYER, K.B., SKOGBERG, M., MARGENFELD, C., IRELAND, J. and PETTERSSON S. 1995. Repression of the IgH 3' enhancer by helix-loop-helix protein Id3 via a functionally important E47/E12 binding site: implications for developmental control of enhancer function. **Eur. J. Immunol. 25**, 1770-1777.

MEYER, K.B., TEH, M-Y. and NEUBERGER, M.S. 1996. The Igκ 3'-enhancer triggers gene expression early in B lymphocytes but its activity is enhanced on B cell activation. **Int. Immunol. 8**, 1561-1568.

For further publications see no. 56.

REGULATION OF TRANSCRIPTION IN DEVELOPING B LYMPHOCYTES



Induction of transcription factor activity after B cell stimulation.

The development of a mature B cell from a haematopoietic stem cell proceeds through a number of distinct stages, defined by the expression of surface markers. Our work has focused on the molecular basis for the tissue-restricted and developmentally controlled expression of some of these surface proteins. In particular, we have studied the control of the immunoglobulin (Ig) genes. Initial experiments examined the transcription factors responsible for the activity of the Igκ 3' enhancer in cell lines. More recently this work has been extended to studying the activity of the κ3' enhancer in transgenic mice. These experiments revealed a function of this enhancer early in B cell development and strong inducibility of the 3' enhancer at the final stage of B cell differentiation. Cells from these animals will now be used to examine the signals and signalling pathways responsible for enhancer activation *in vivo*. *In vitro* studies have examined which transcription factors may play a role in enhancer induction. In particular, we have identified a binding site for a NF-AT related factor, whose activity is induced upon B cell activation by treatment with ionomycin and PMA.

In addition we have initiated experiments to examine the lymphoid-specific expression of the interleukin-7 receptor α chain. In the B lineage this gene is expressed in a defined developmental window before surface Ig expression, and is required for normal early lymphoid development.

JONATHON PINES

PAUL CLUTE

MARK JACKMAN

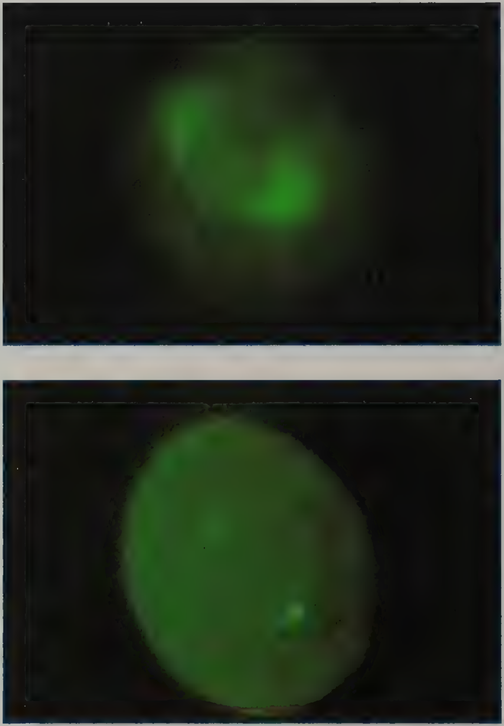
CHRISTINA KARLSSON

TUNKIAT KO

ANNA MEDDINS

LUCY PERKINS

KAREN SIMPSON



Cyclin B1 and GFP-Cyclin B1 bind the mitotic spindle.

Top: Endogenous cyclin B1 visualised in a fixed cell with anti-cyclin B1 antibodies
Bottom: GFP-Cyclin B1 visualised in a living metaphase cell.

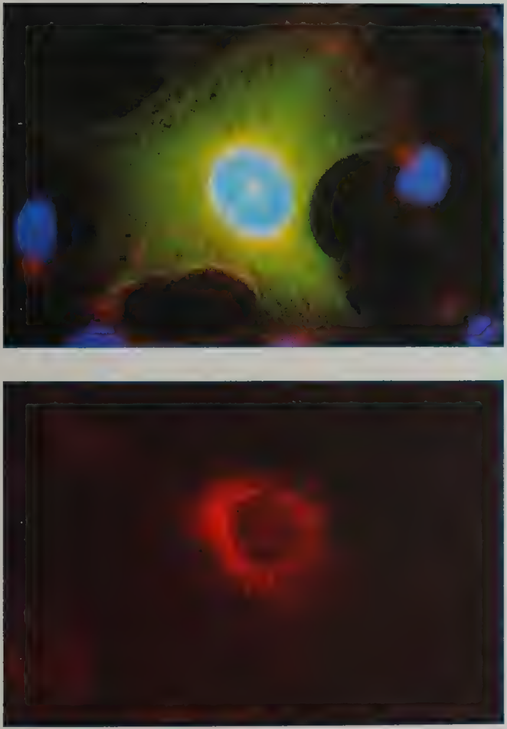
PINES, J. and HUNTER, T. (1994). 'The differential localisation of human cyclins A and B1 is due to a cytoplasmic retention region in cyclin B1'. **EMBO J. 13,** 3772-3781.

JACKMAN, M., FIRTH, M., and PINES, J. (1995). 'Human cyclins B1 and B2 are localised to strikingly different structures: B1 to microtubules, B2 primarily to the Golgi apparatus'. **EMBO J. 14**, 1646-1654

PINES, J. (1995). 'GFP in mammalian cells'. **Trends Genet., 11**, 326-327.

For further publications see no. 80.

REGULATION OF THE MAMMALIAN CELL CYCLE BY CYCLIN-DEPENDENT KINASES



Top: Cell stained with anti-cyclin B1 (green)
Bottom: Cell stained with anti-cyclin B2 (red)

Cyclin B1 and B2 localised to different sub-cellular structures. It is clear that cyclin B1 binds to microtubules and cyclin B2 localises to the golgi and vesicle compartment

The cell cycle ensures that DNA replication and mitosis are discrete and sequential. It is orchestrated by the cyclin-dependent kinases (CDKs) that are activated and localised to the correct sub-cellular structures by their cyclin partner.

We are studying how cyclins localise CDKs to particular parts of the cell. Cyclin A targets CDK1 and CDK2 to the nucleus, whereas cyclin B1 targets CDK1 to the cytoskeleton and cyclin B2 directs it to the Golgi apparatus and the ER. This facet of the cyclins may be responsible for co-ordinating the dramatic changes in cell structure at mitosis.

Using chimaeric proteins and point mutants we have defined the regions of the cyclins required for their localisation. We have found a number of proteins that are able to interact specifically with these regions through the yeast 2 hybrid screen, and are determining their physiological role in cell cycle regulation.

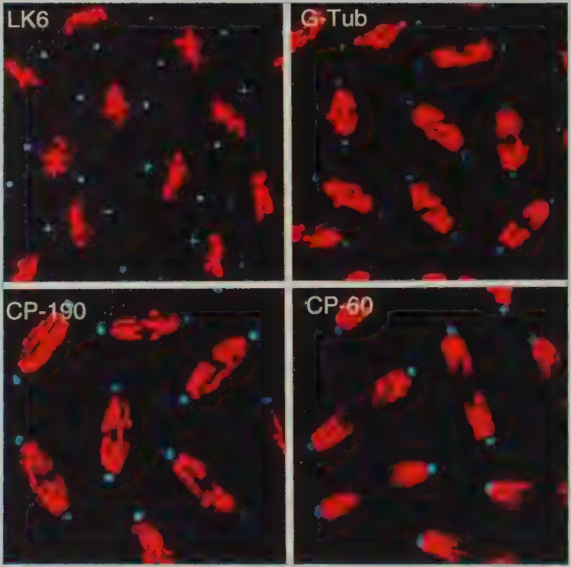
We have extended our studies on protein localisation by using green fluorescent protein (GFP) as an in vivo marker for cyclin localisation. Cyclin-GFP chimaeras are correctly localised, and we are able to observe them in living cells as they progress through the cell cycle. By generating a more complete description of the interactions between cell cycle regulators in both space and time in living cells, we hope to deepen our understanding of how cells co-ordinate growth, DNA synthesis and cell division.

JORDAN RAFF

JUNYONG HUANG

DEBORAH KIDD

JAMES WAKEFIELD



Centrosomes (blue) and chromosomes (red)
during mitosis in an early Drosophila *embryo.*

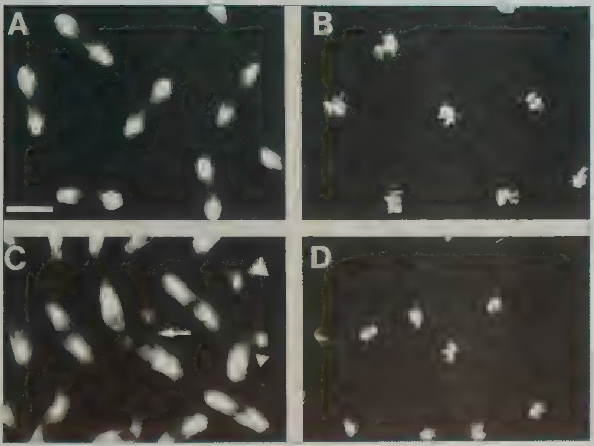
RAFF, J.W. 1996. Centrosomes and microtubules: wedded with a ring. **Trends Cell Biol. 6**, 248-251.

KELLOGG D.R., OEGEMA, K., RAFF, J., SCHNEIDER, K., and ALBERTS, B.M. 1995. CP60: a microtubule-associated protein that is localised to the centrosome in a cell-cycle specific manner. **Mol. Biol. Cell 6**, 1673-1684.

For further publications see no. 40, 42, 66.

MOLECULAR ANALYSIS OF THE CENTROSOME

The centrosome is the main microtubule organising centre in animal cells. Despite its central importance in organising many cellular events, very little is known about its molecular structure. We have isolated a number of proteins that bind to microtubules in vitro and are associated with the centrosome in vivo, thus making them good candidates for proteins involved in the interaction between centrosomes and microtubules.



Microtubules (left hand panels) and chromatin (right hand panels) in a normal embryo (A,B), and in an embryo over-expressing the LK6 kinase (C,D). Arrows highlight regions where mitotic defects are occurring.

One of these proteins is a novel protein kinase called LK6. This protein contains a PEST sequence and is rapidly turned over in the embryo. Flies overexpressing the LK6 kinase are very sick, and show a variety of mitotic defects in the early embryo (see figure), while overexpressing a mutated LK6 protein that has no kinase activity is without effect. Our current hypothesis is that overexpressing the LK6 protein makes microtubules too stable in the embryo. A second protein, CP60, is located mainly in the nucleus in interphase and relocates to the centrosome during mitosis. Phosphorylation by cdc2/cyclin B regulates the ability of this protein to interact with microtubules in vitro, and we are currently testing the role of this phosphorylation event in vivo. We have also isolated two new centrosomal MAPs this year, both of which appear to have mammalian homologues of unknown function.

We are using a variety of molecular, biochemical, cell biological, and genetic approaches to study the functions of these centrosomal proteins.

Daniel St Johnston

JAN ADAMS

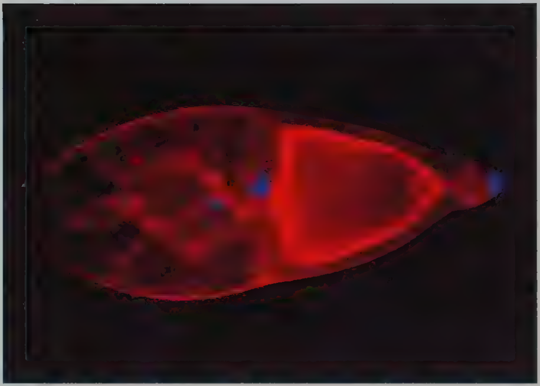
FREDERICUS VAN EEDEN

HEATHER ELLIOT

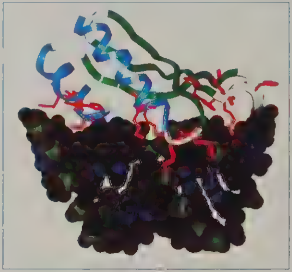
ACAIMO GONZÁLEZ-REYES

RUTH McCAFFREY

RACHEL SMITH



Gurken encodes the signal that induces posterior follicle cell fate. In gurken mutants, the anterior follicle cell marker slbo (blue) is expressed in the follicle cells on both the anterior and posterior sides of the oocyte. The positions of the oocyte, nurse cells and follicle cells are indicated by Rhodamine-phalloidin staining (red) of the actin cytoskeleton



A model for how a single double-stranded RNA binding domain from Staufen protein contacts dsRNA. The backbone of the domain is shown as a ribbon with α helices in blue, β sheets in green, and loops in white. The side chains of the amino acids that are required for RNA-binding are shown in red, and all project from one side of the domain. The model shows how these side chains might contact a 12 base pair region of dsRNA (bottom)

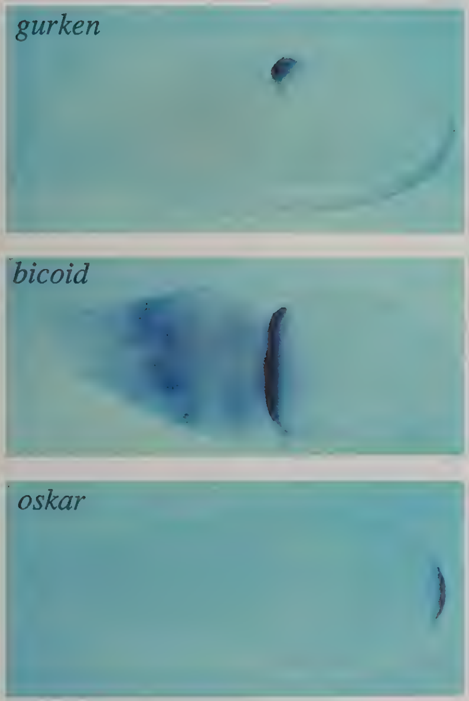
GONZÀLEZ-REYES, A., ELLIOTT, H. and ST JOHNSTON, D. 1995. Polarization of both major body axes in *Drosophila* by *gurken-torpedo* signalling. **Nature 375**, 654-658.

ST JOHNSTON, D. 1995. The intracellular localisation of messenger RNAs. **Cell 81**, 161-170.

GRÜNERT, S. and ST JOHNSTON, D. 1996. RNA localisation and the development of asymmetry during *Drosophila oogenesis.*

Current opinion in Genetics and **Development 6**, 395-402

mRNA LOCALISATION AND THE ORIGIN OF POLARITY IN DROSOPHILA



The localisation of gurken, bicoid and oskar mRNAs to three distinct positions within the Drosophila oocyte. The accumulation of gurken mRNA in the dorsal/anterior corner of the oocyte establishes dorsal-ventral polarity, while the localisation of bicoid and oskar mRNAs to opposite poles determines the anterior-posterior axis.

The intracellular localisation of mRNA is a general mechanism for protein targeting which is now thought to occur in all polarised cell types. A striking example of this phenomenon is provided by the *Drosophila* oocyte, where the localisation of *bicoid*, *oskar*, and *gurken* mRNAs to three distinct positions within the cell determines the polarity of the anterior-posterior and dorsal-ventral axes of the embryo. We are taking several approaches to investigate how these mRNAs are transported within the oocyte in order to understand both the mechanism of mRNA localisation and the origin of polarity.

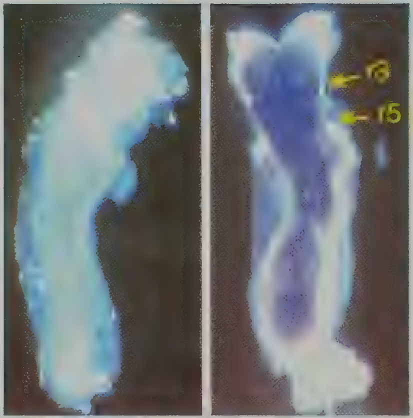
1) Staufen protein is required for the localisation and translational control of both *bicoid* and *oskar* mRNAs, and co-localises with each transcript. We have identified a novel dsRNA-binding domain that occurs five times within Staufen, and are now studying how these domains allow the protein to recognise two distinct mRNAs.

2) We are carrying out genetic screens to identify other genes involved in mRNA localisation, in particular the motor proteins that transport these transcripts.

3) We have recently shown that anterior-posterior polarity originates from the movement of the oocyte to the posterior of the egg chamber, and the subsequent induction of posterior fate in the adjacent follicle cells. We are currently cloning two genes that are required for oocyte migration.

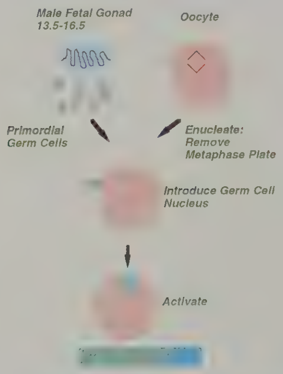
AZIM SURANI

JUSTIN AINSCOUGH
SAM APARICIO
SHEILA BARTON
JAMES BRENTON
ROBERT DREWELL
KELVIN HAWKER
KATHY HILTON
ROSALIND JOHN
NOBUAKI KIKYO
LOUIS LEFEBVRE
LI-LAN LI
MAITHREYI NARASIMHA
YUK-YEE SZETO
MASAKO TADA
TAKASHI TADA



Expression of Xnat in d8.5 mouse: No expression is detected in parthenogenetic (PG) embryo. In normal embryos, strong expression is seen in rhombomeres, r3 and r5.

Reconstitution of oocyte with male germ cell nucleus


Male Fetal Gonad
13.5-16.5
Oocyte
Primordial Germ Cells
Enucleate: Remove Metaphase Plate
Introduce Germ Cell Nucleus
Activate

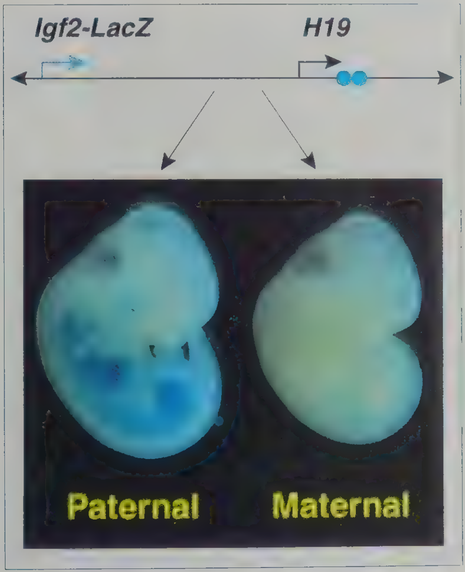
DEVELOPMENT IS INFLUENCED BY EPIGENETIC CHANGES IN THE GERM LINE

JOHN, R.M. and SURANI, M.A. 1996. Imprinted genes and regulation of gene expression by epigenetic inheritance. **Current Opinion in Cell Biology 8,** 348-353.

KUROIWA, Y., KANEKO-ISHINO, T., KAGITANI, F., KOHDA, T., LI, L-L., TADA, M., SUZUKI, R., YOKOYAMA, M., SHIROISHI, T., WAKANA, S., BARTON, S.C., ISHINO, F. and SURANI, M.A. 1996. *Peg3* imprinted gene on proximal chromosome 7 encodes for a zinc finger protein. **Nature Genetics 12,** 186-190.

For further publications see no. 1, 41.

MAMMALIAN DEVELOPMENT: SIGNIFICANCE OF EPIGENETIC DETERMINANTS INHERITED FROM THE GERM LINE



Imprinting of Igf2LacZ/H19 YAC clone showing preferential LacZ expression after paternal transmission.

Mammalian development is regulated by epigenetic determinants that are inherited from the germ line. This accounts for the functional differences between parental genomes during development caused by the preferential expression of one parental allele of genes called imprinted genes. We are investigating the germ line to understand the molecular nature of the epigenetic determinants and their consequences for development and disease.

We aim to identify the *cis* elements that confer imprinting on individual and clusters of imprinted genes within large domains. We are also attempting to identify the *trans*-acting genes that induce appropriate epigenetic modifications at imprinted loci. Conditional deletion of these *cis* elements and *trans*-acting genes, in germ cells, gametes and embryos, will establish their precise functions at critical stages of the imprinting cycle.

Another aim is to identify imprinted genes systematically and to understand their precise functions during development. Some novel imprinted genes such as *Nnat*, *Peg3* and *Peg1* that influence early embryonic development as well as behaviour are the focus of our current investigations.

ENRIQUE AMAYA

MATTHEW POLLI

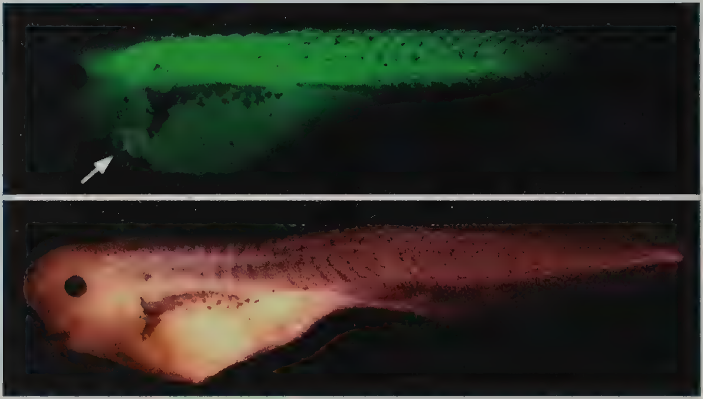


Figure 1. Transgenic embryo expressing GFP from a muscle and heart specific promoter. Arrow shows expression in the heart.

KROLL, K.K. and AMAYA, E. (1996) Transgenic Xenopus embryos from sperm nuclear transplantations reveal FGF signaling requirements during gastrulation. **Development** 122:3173-3183.

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For further publications see no. 55.

SIGNALS THAT ORGANISE THE VERTEBRATE EMBRYO

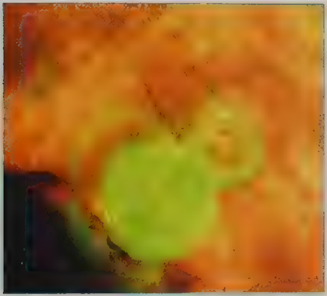


Figure 2. GFP expression in the heart of transgenic embryo.

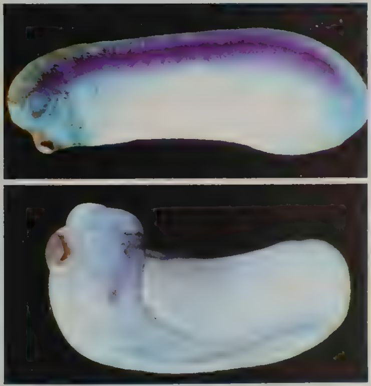
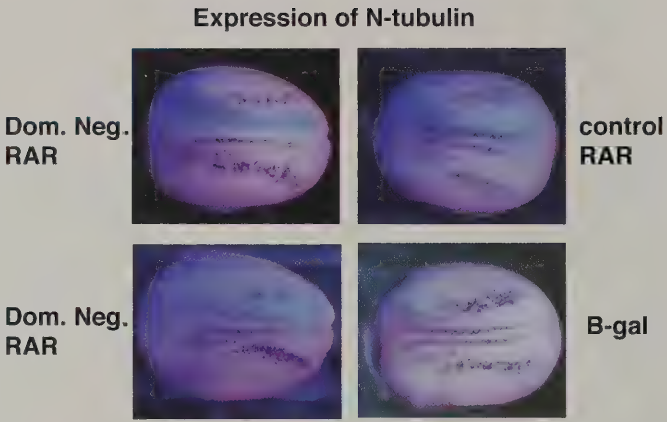


Figure 3. Transgenic embryos expressing a control (upper) or dominant negative FGF receptor (lower) and stained for a notochord and somite marker. Blocking signalling through the FGF receptor results in embryos lacking notochord or muscle.

The vertebrate embryo is organized and patterned following a series of inductive events. The first of these signalling events results in the formation of the mesoderm at the blastula stage. The second event occurs at the gastrula stage when the dorsal mesoderm patterns the rest of the mesoderm. As a long term goal we would like to understand the molecular basis of the inductions that organise the vertebrate embryo. In addition we would like to better understand how localised production of signalling molecules gets translated into organised changes in cell movement and differentiation.

We are interested in determining how secreted molecules act in a concerted way, in space and time, to produce a fully organized embryo. To this end we have been investigating the role of fibroblast growth factor (FGF) during mesoderm formation in the frog, Xenopus laevis. We have found that inhibiting FGF signalling in the embryo, by expressing a dominant negative version of the FGF receptor, disrupts mesoderm formation. In addition by following the morphogenetic movements that occur during the gastrula and neurula stages using time-lapse video microscopy, we are studying the signalling events that pattern the embryo as they occur. Finally we recently developed a very efficient method for making transgenic frog embryos. This technology will allow us to manipulate the expression of developmental genes in the embryo with much better precision than ever before.

NANCY PAPALOPULU



*In situ hybridisation analysis of neural plate stage Xenopus embryos injected with Dominant Negative or a Control truncated Retinoic Acid Receptor (Dom. Neg. RAR and Control RAR, respectively). B-gal RNA was co-injected as a lineage tracer. Injection of the Dom. Neg. RAR RNA eliminates or greatly reduces primary neurons, as marked by N-tubulin expression, while Control RAR or B-gal RNA alone has no effect. (see no. *)*

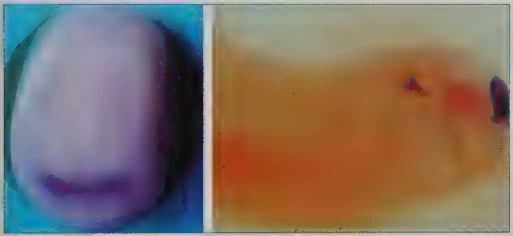
PAPALOPULU, N. and KINTNER, C. (1996). A novel *Xenopus* homeobox gene, *Xbr-1* defines a novel class of homeobox genes and is expressed in the dorsal ciliary margin of the eye. **Developmental Biology 173:** 104-114.

PAPALOPULU, N. and KINTNER, C. (1996). Anteroposterior patterning controls the timing of neuronal differentiation in *Xenopus* embryos. **Development 122:** 3409-3418.

For further publications see no. 6, 63, 64.

MOLECULAR CONTROL OF NEUROGENESIS AND NEURAL PATTERNING IN XENOPUS EMBRYOS

Neural induction in *Xenopus* embryos requires inductive interactions between the ectoderm and a mesodermal region of the embryo, called Spemann's organiser. A process that is closely linked to neural induction is the process of regionalisation or patterning, whereby the neural ectoderm is divided into regions with distinct developmental fates. We have shown that this patterning process controls the position and timing of primary neuron differentiation within the neural plate. We are interested in identifying the molecular nature of the signals that are involved in patterning and neurogenesis and to understand how these two processes are integrated. By expressing a dominant negative form of a retinoic acid receptor in whole *Xenopus* embryos we have shown that retinoid signalling is necessary *in vivo* for correct anteroposterior patterning and neuronal differentiation.



XBF-1 expression marks the developing telencephalon in Xenopus embryos (right), as early as the neural plate stage (left).

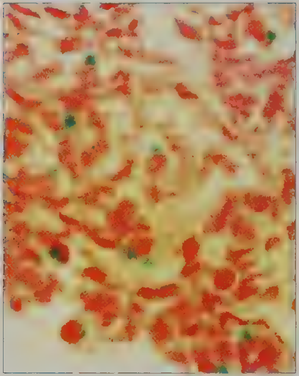
We are currently working to identify additional factors and to this end, we have designed functional screens that will specifically identify signals or intracellular determinants that posteriorise and/or induce neuronal differentiation. In addition, we have characterised a number of regionally-restricted transcription factors such as XBF-1, a telencephalon-specific, winged-helix transcription factor and *Xbr-1*, a novel homeobox gene, and we are currently manipulating the expression of these genes to investigate their role in patterning and neurogenesis.

ANNE McLAREN

GERM CELLS IN THE MOUSE

JULIE MERRIMAN

Embryonic germ cells, the cells whose descendants give rise to eggs in the female, sperm in the male, move from the extra-embryonic region where they are located during gastrulation, to the genital ridges, the site of the future gonads. Once in the genital ridges, germ cells in female embryos enter meiotic prophase and develop as oocytes.



x100

Germ cells from a 13.5 day female embryo carrying a lac-Z transgene, developing in a cultured male genital ridge reaggregate. Note the intense blue spot in each donor germ cell.

In male embryos, on the other hand, the first spermatogenic cells do not enter meiosis until a week after birth. However, if they are removed sufficiently early from the male genital ridge environment, they too will enter meiosis and develop as oocytes. By explanting germ cells into cultured reaggregates of embryonic lung, we have identified the critical time for commitment to spermatogenesis

Our studies suggest that the timing of entry into meiosis depends on the germ cells themselves rather than on the surrounding tissue.

Cultured in the presence of appropriate growth factors, mouse embryonic germ cells will give rise to stem cell (EG cell) lines that proliferate indefinitely in vitro. We are studying the fate of EG cells explanted into cultured reaggregates of either embryonic lung, or male or female genital ridges .

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SCIENTIFIC STAFF OF THE INSTITUTE

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PRINCIPAL GROUP LEADER	Professor/Reader/Lecturer Level
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LABORATORY ASSISTANT	Within individual groups or part of Core support; grant-funded

POSTGRADUATE OPPORTUNITIES

As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of a Biological or Medical Sciences Department with which their group is affiliated.

Graduate studentships are supported mainly by the Wellcome Trust or the Cancer Research Campaign but additional sponsorship may be applied for from a variety of sources, including the Government Research Councils.

Applicants should write, in the first instance, to the leader of the group whose work interests them.

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INSTITUTE PUBLICATIONS

1 ANDERMARCHER, E., SURANI, M.A., and GHERARDI, E. 1996. Co-expression of the *HGF/SF* and c-met genes during early mouse embryogenesis precedes reciprocal expression in adjacent tissues during organogenesis. **Developmental Genetics 18**, 254-266.

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OTHER ACTIVITIES

MICHAEL AKAM is a member of the Wellcome Cell & Molecular Biology Board.

CHARLES FFRENCH-CONSTANT is a Consultant in Medical Genetics at Addenbrooke's Hospital, Cambridge.

JOHN GURDON is currently a member of the Council of the Cancer Research Campaign, and is a Governor of the Wellcome Trust.

STEVE JACKSON is a member of the Biochemical Society Nucleic Acids and Molecular Biology Group Committee, and a member of the Biochemical Society Council.

TONY KOUZARIDES is a member of the Cancer Research Campaign Grants Committee.

RON LASKEY is President of the British Society of Cell Biology, a member of the Cancer Research Campaign Scientific Committee, and a Trustee of Strangeways Research Laboratories.

ANNE McCLAREN is Foreign Secretary of the Royal Society.

HONOURS AND AWARDS

JOHN GURDON delivered the Royal Society's Rutherford Memorial Lecture, in several cities in Australia, in September 1996.

STEVE JACKSON was awarded the Colworth Medal of the Biochemical Society and the 1997 Tenovus Medal.

RON LASKEY was awarded the CIBA Medal of the Biochemical Society.

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